REMARKS/ARGUMENTS

Claims 2-4 and 7-10 remain cancelled.

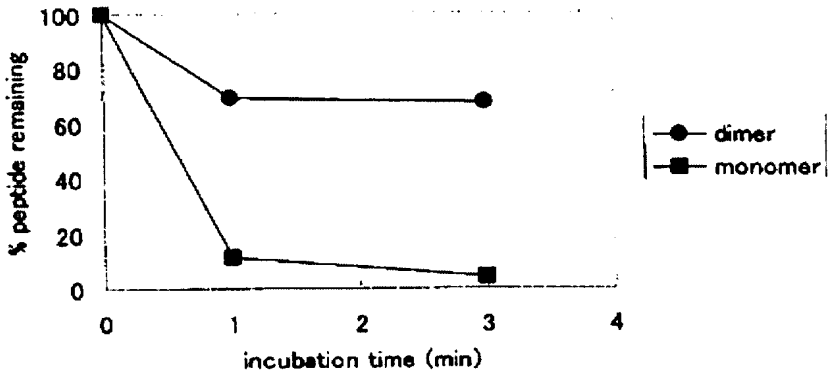
Because the claims have not been amended, no new matter has been added.

Applicants respectfully traverse the obviousness rejection of Claims 1 (in part), 5, 6 and 11, as being unpatentable in view of EP 1103564 ('564) or EP 1371664 ('664) or Gaiger in view of Di Modungo.

The Office has rejected Claims 1, 5, 6 and 11, in view of the combination of non-dimerized sequences in one of '564, '664, or Gaiger in combination with Di Modungo. At the outset, Applicants traverse this rejection on the basis of a superior and unexpected results.

As described in the Declaration Under 37 C.F.R. § 1.132 filed on January 18, 2008, and executed by Dr. Haruo Sugiyama, M.D. Ph.D., in Experiment 2, pages 3 and 4 of the Declaration, monomer and homodimer of the peptide (SEQ ID NO: 44) were placed in mouse serum and the percentage of both monomer and homodimer remaining in the mouse serum was measured by reverse phase high performance liquid chromatography at the time of addition of the monomer and homodimer to the mouse serum, and at 1 and three minutes thereafter. The results of these measurements are presented in Figure 2 of the Declaration, reproduced below:

Figure 2



As can be seen in Figure 2, at both the 1 and 3 minute marks, the % of homodimer (e.g., dimer) remaining was significantly higher (at least 60% higher at 1 minute and approximately 60% higher at 3 minutes) than the % of monomer (e.g., monomer) remaining. Thus, the stability of homodimer in plasma was far superior to the stability of monomer.

Stability is blood / plasma is a very important property for a vaccine, and particularly for a cancer vaccine. Applicants submit this superior result of enhanced homodimer stability in blood / plasma is not described or suggested by any of ('564), ('664), Gaiger or Di Modungo, either alone or in combination. Based on the failure of ('564), ('664), Gaiger and Di Modungo to describe or suggest enhanced homodimer stability in blood / plasma, this superior result is an unexpected result.

Applicants submit this superior and unexpected result is exactly the type of secondary consideration envisioned by the MPEP to address a *prima facie* case of obviousness. Withdrawal of the obviousness rejection is requested on this basis alone.

The obviousness rejection is respectfully traversed on the basis of a second superior and unexpected result.

As described in the Sugiyama Declaration at pages 2 and 3, the peptide dimer induced CTL's that recognized the natural type-peptide monomer. As described in Di Modugno, Summary, page 341, "Small peptides 8-10 amino acids long,...are usually presented and recognized by CD8+ cytolytic T lymphocytes (CTL's) associated with major histocompatability complex (MHC) class I molecules." Thus, a small 8-10 amino acid peptide forms a complex with an MHC Class I antigen and is thereby recognized by CTL's.

Applicants note, however, that dimers and monomers have different structures.

The Applicants discovered that CTL's induced by a dimer subsequently recognized a monomer; and, that CTL's induced by the dimer had a cross-reactivity and recognized the natural-type peptide monomer (underlining emphasis added). Applicants note that a peptide dimer would be expected to lack therapeutic activity if CTL's induced by administration of the peptide dimer did not recognize a peptide monomer, specifically a natural type peptide monomer, because cancel cells in a living body present a peptide monomer of the natural type.

Applicants respectfully submit the superior result that dimer induced CTL's recognition of and cross-reactivity to the peptide monomer of the natural type is not described or suggested by the cited references, either alone, or in combination. Accordingly, this superior result, based on the teachings of the cited references, is an unexpected result.

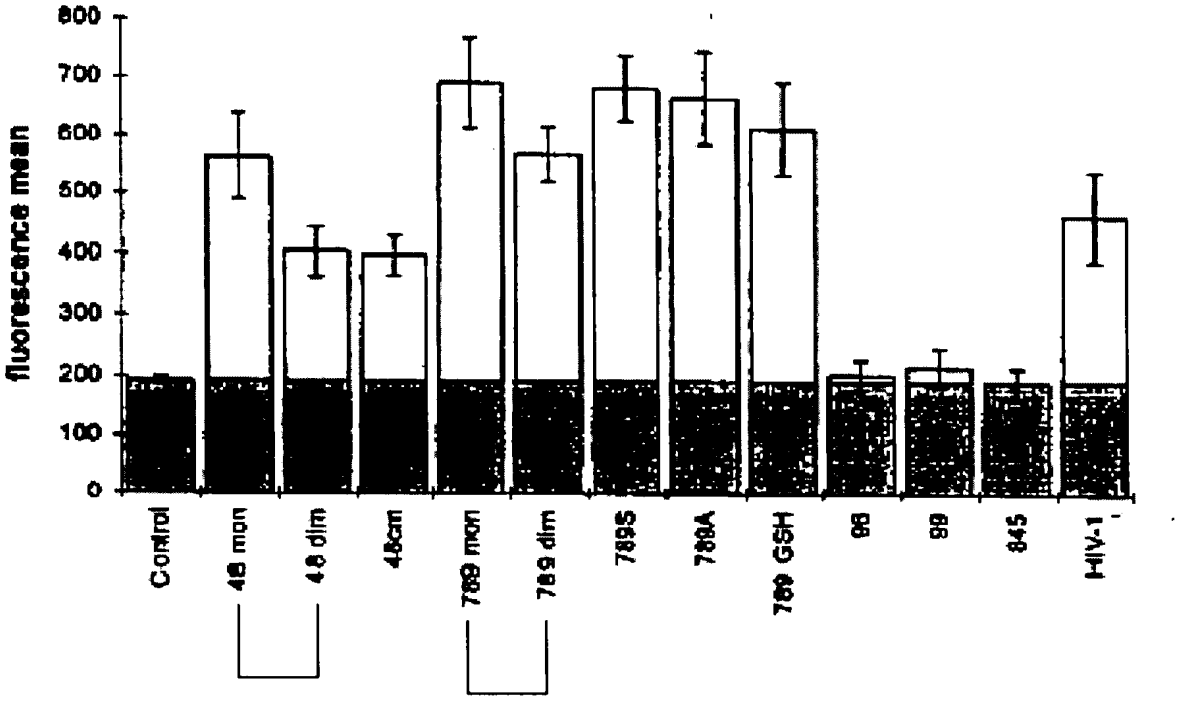
Applicants submit this superior and unexpected result is exactly the type of secondary consideration envisioned by the MPEP to address a *prima facie* case of obviousness. Withdrawal of the obviousness rejection is requested on this basis alone.

Additionally, the Office has argued, at pages 5-6 of the Official Action, that "The only difference between these references ['564, '664, and Gaiger] and the instant invention is the dimerization using a disulfide bond"; that "Di Modugno discloses the use of homodimers to form disulfide bonds in homodimers and that this increases the generation of different conformations which can lead to increased anti-tumor response"; and that "As seen in figure 2 [of Di Modugno] there is increased binding in both 48 dim and 789 dim as compared to control. In view of the binding and the view of the fact that applicant's claims are product claims, it is expected that the homodimers of the reference can induce CTL activity".

Applicants respectfully submit the Office's reasoning is flawed.

Di Modugno does not examine CTL-inducing activity. Di Modugno examines only binding affinity to HLA-A2. In Figure 2, the Office has inappropriately compared binding affinity of dimers 789 dim and 48 dim to control. In fact, the Office should have compared binding affinity of the dimers 789 dim and 48 dim to the monomers 48 mon and 789 mon.

Figure 2 of Di Modugno has been reproduced below with added emphasis lines at the bottom of the figure:



As can be seen in Figure 2, the monomer (48 mon) has a higher affinity than the dimer (48 dimer) and the monomer (789 mon) has a higher affinity than the dimer (789 dim). Accordingly, there would be no expectation of increased activity based on the increased binding affinities of the dimers when compared to the monomers, because the dimers have significantly reduced binding affinity as compared to the monomers.

Further, the Office, as described above, states "Di Modugno discloses the use of homodimers to form disulfide bonds in homodimers and that this increases the generation of

different conformations..." and "In view of the binding and the view of the fact that applicant's claims are product claims, it is expected that the homodimers of the reference can induce CTL activity."

In the present case, given that the binding affinity of the homodimers is lower than the binding affinity of the monomers in Di Modugno, and given that as described by the Office and Di Modugno, the formation of homodimers through disulfide bonds "increases the generation of different conformations," many of which would be expected to not be biologically active, it is not expected that "homodimers of the reference can induce CTL activity."

Indeed, Di Modugno, either alone or in combination with the other cited references, does not describe or suggest that CTL's induced by a homodimer could recognize and attach a cancer cell presenting the corresponding monomer, absent hindsight provided by the Applicant's disclosure.

Further, just because a compound binds to a receptor, there is no way, *a priori*, to predict if that compound will, for example, result in activating the receptor (e.g., be an agonist), partially activate the receptor (e.g., be a partial agonist), partially antagonize the receptor (e.g., be a partial antagonist), fully antagonize the receptor (e.g., be a full antagonist), act as both an antagonist and agonist (e.g., be a partial agonist/partial antagonist), or have no functional activity at all.

Applicants submit that the Office has failed to show why one of ordinary skill in the art would be able to expect that a peptide homodimer, that according to De Modugno has significantly less binding affinity than the monomer, and different and multiple confirmations, would induce CTL recognition of and cross-reactivity to the peptide monomer

of the natural type. In short, there is an absence of linkage between binding activity and biological activity in the Office's argument.

Applicants submit there is, therefore, insufficient expectation of success combining the references the Office is attempting to combine and that sufficient reason to combine the references has not been provided.

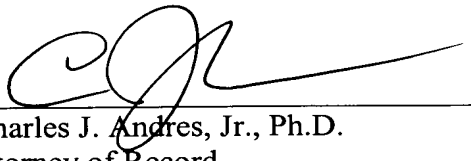
Withdrawal of the obviousness rejection is respectfully requested.

Applicants submit the present application is now in condition for allowance.

Early notification to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



Charles J. Andres, Jr., Ph.D.
Attorney of Record
Registration No. 57,537

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 08/07)